

## Very aggressive gastric adenocarcinoma with rare osteoclast — like giant cells: a case report and review of the literature

Barbara Rygoł<sup>1</sup>, Kamil Wdowiak<sup>1</sup>, Jacek Pająk<sup>2</sup>, Jerzy Wojnar<sup>1</sup>, Jerzy Chudek<sup>1</sup>

Extraskelatal carcinomas with osteoclast-like giant cells (OGC) constitute a rare type of malignant tumors, usually located in the pancreas, gall bladder, breast and kidney. Histologically they are characterized by the presence of multinucleated giant cells that resemble osteoclasts mixed with poorly differentiated adenocarcinoma cells. This paper reports a case of primary gastric adenocarcinoma with osteoclast-like giant cells in a 75-year-old woman who suffered from epigastric pain, nausea, vomiting and weight loss. Histological examination of the tissue obtained during initial surgery (subtotal palliative Billroth II resection) revealed poorly differentiated adenocarcinoma with an infiltrate of osteoclast-like giant cells and no EBV immunostaining (non-lymphoepithelioma-like carcinoma, stage pT4aN3a). The tumor progressed rapidly with extensive perigastric involvement, infiltration of the paraaortic lymph nodes and the head of the pancreas. Poor general condition (WHO 3) prevented postoperative chemotherapy. The patient died 5 months after surgery due to rapid relapse. There is still a lack of knowledge to determine the prognosis for patients with OGC carcinomas. In this study, we report a case of gastric adenocarcinoma with OGC and review the previously published literature clinical and pathologic data on this rare neoplasm.

Biuletyn PTO NOWOTWORY 2018; 3, 2: 103–106

**Key words:** osteoclast-like giant cells, CD 68, adenocarcinoma, stomach

### Introduction

Adenocarcinomas with osteoclast-like giant cells, that are typical for osseous neoplasms, are extremely rare tumors with usually slow growth, a relapse rate of 50% after surgery, and low metastatic potential. Undifferentiated carcinomas with OGC were first described by Rosai in 1968 and classified by WHO in 2000 [1]. According to the literature, these tumors are often discovered in the breast [2], pancreas [3], endometrium [4], gallbladder [5] osteoclast-like giant cells (OGCs, thyroid [6] and lungs [7]. Until the present, only few cases of gastric adenocarcinomas with OGC, usually poorly differentiated have been reported, mostly in men (Tab. I). They were located mainly in the gastric cardia or corpus.

### Case description

A 75-year old female was admitted to the Surgical Department in January 2013 reporting upper abdominal pain, nausea and vomiting. There was no history of hematochezia or melena, but she had lost 6 kg in weight in 2 months. Physical examination revealed mild tenderness in the epigastric region of the abdomen. Laboratory tests showed anemia (Hb 7.8 mmol/l) with iron deficiency (Fe 8.1 μmol/l). An abdominal CT scan demonstrated a large mass 15 × 10 cm infiltrating the lesser curvature of the stomach, antrum and duodenum without lymph node involvement. Esophagogastrosocopy revealed an ulcerative lesion of 5 cm diameter in the antrum as well as blood clots

<sup>1</sup>Department of Internal Medicine and Oncology, School of Medicine in Katowice, Silesian Medical University, Katowice, Poland

<sup>2</sup>Department of Pathology, School of Medicine in Katowice, Silesian Medical University, Katowice, Poland

#### Artykuł w wersji pierwotnej:

Rygoł B, Wdowiak K, Pająk J, Wojnar J, Chudek J. Very aggressive gastric adenocarcinoma with rare osteoclast — like giant cells: a case report and review of the literature. *NOWOTWORY J Oncol* 2018; 68: 97–100.

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on the surface of the lesser curvature. A subtotal palliative Billroth II resection was performed without preoperative chemotherapy. Pathology found an exophytic tumor with necrosis located in the antrum 5 cm in diameter. Gastric folds were smoothed as the tumor invaded through the seromuscular layer and infiltrated the perigastric adipose tissue as well as the duodenum. Metastatic infiltrates were found in 11 of 13 identified local lymph nodes (diameter up to 1.5 cm) — stage pT4aN3a.

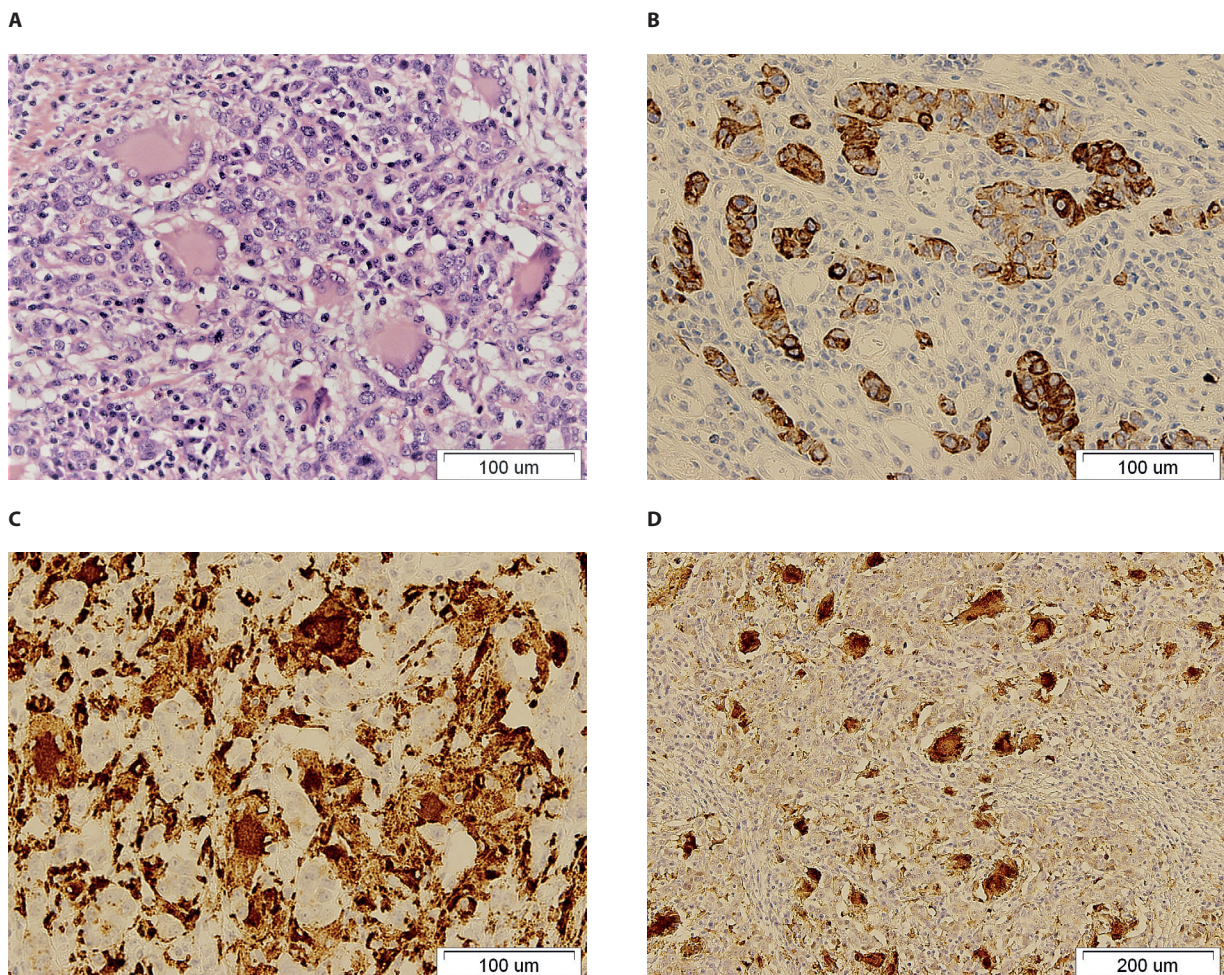
Histological assessment showed a poorly differentiated adenocarcinoma with an infiltrate of osteoclast-like giant cells (Fig. 1). Neoplastic cells were positive for CK 7, AE1/AE3+, EMA+/- and negative for vimentin, synaptophysin, CD 31, CD 20, CD 99, HCG, EBV (LMP-1) and Her-2, while OGCs were positive for CD68+ and lysozyme. Immunohistochemical staining was performed using antibodies from Dako and Roche (for Her-2). The OGC were present both in the primary gastric adenocarcinoma and lymph node metastases. CD 3, CD 4 T-lymphoid cells infiltrates were observed in tumor stroma.

A postoperative CT scan (April 2013) revealed a cancer infiltration of the pancreas head and enlargement of the

para-aortic lymph nodes. Poor general condition (WHO 3), jaundice (serum bilirubin level 80–122  $\mu\text{mol/l}$ ) with elevated activities of GGTP (460–680 IU/l) and ALP (359–560 IU/l) precluded chemotherapy. There was rapid local progression with extensive perigastric involvement. The patient died 5 months after surgery.

## Discussion

Gastric carcinomas with OGC are a heterogeneous group of tumors. Ushiku et al. described three distinct types of gastric carcinomas with OGC: lymphoepithelioma — like carcinoma (LELC), non-LELC, and giant cell tumor (GCT) [8]. According to the authors, the LELC type is associated with Epstein-Barr Virus (EBV) infection, that could be confirmed by RNA in situ hybridization (ISH) and granulomatous reaction with OGC, forming small clusters of epithelioid histiocytes or sarcoidal granuloma. In contrast, non-LELC cases are not associated with EBV infection or possibly loose viral DNA in the cancer progression [8]. In addition to OGC, infiltrations with neutrophils, macrophages and lymphoplasmacytic cells were reported. The GCT type is characterized by numerous OGC with metaplastic



**Figure 1.** Poorly differentiated adenocarcinoma of the stomach: **A:** with multinucleated giant cells. H-E stain  $\times 200$ ; **B:** positive for cytokeratin CK7. IHC stain  $\times 200$ ; **C:** positive CD 68 staining on the OGC and stromal macrophages, IHC  $\times 200$ ; **D:** positive lysozyme staining in multinucleated giant cells. IHC  $\times 100$

**Table I.** Summary of reported cases with gastric carcinoma with OGC (N = 18)

Age	Gender	Tumor Stage	Tumor type	Therapy	Postoperative follow-up	Ref.
81	Male	T1b N0 M0	non-LELC	Subtotal gastrectomy	> 12 months	[11]
69	Male	T1 N0 M0	LELC	Partial gastrectomy	Unknown	[8]
69	Male	T3 N0 M0	LELC	Distal gastrectomy	Unknown	[8]
50	Male	T3 N0 M0	LELC	Initial surgery	> 3 months	[12]
63	Male	T2 N1 M0	LELC	Subtotal gastrectomy	> 120 months	[13]
61	Male	T2 N1 M0	LELC	Subtotal gastrectomy	+ after 15 months	[13]
76	Male	T2 N1 M0	LELC	Subtotal gastrectomy	+ after 13 months	[13]
71	Male	T2 N1 M0	LELC	Total gastrectomy	> 57 months	[8]
65	Male	T2 N1 M0	non-LELC	Distal gastrectomy	> 102 months	[8]
64	Male	T3 N1 M0	LELC	Total gastrectomy	> 7 months	[8]
86	Male	T4 N1 M0	GCT	Palliative gastrectomy	Unknown	[8]
84	Male	T2 N1 M0	non-LELC	Distal gastrectomy	> 74 months	[8]
64	Female	T1 N2 M0	non-LELC	Distal gastrectomy	> 12 months	[10]
53	Male	T2 N2 M0	LELC	Subtotal gastrectomy	+ after 24 months	[13]
70	Female	T3 N2 M0	LELC	Total gastrectomy	Unknown	[9]
78	Male	T3 N2 M1	non-LELC	Total gastrectomy	> 6 months	[14]
73	Female	pT3 N3a M1 (liver)	GCT	Initial surgery	Unknown/ Fast PD	[15]
75	Female	T4a N3a M1 (lymph nodes)	non-LELC	Subtotal gastrectomy	+ after 5 months	Current case

bone formation [8]. In most described cases, authors suggested a histocytic origin of OGC, due to the positive expression of CD68 [8, 9]. These cells can be found in tumor tissues, metastatic lymph nodes and in the stroma. Presumably, OGC could be part of the immune response to tumor tissue antigens. An unanswered question is whether such neoplasms (with OGC infiltrates) are more aggressive than adenocarcinomas without OGC. Some authors have suggested that the LELC subtype is associated with a better prognosis [10], however available literature reports cases with both good and poor prognosis (Tab. I). The average age was 69 years, which is close to the age of cancer patients without OGC cells (median age 68). The majority of cases (78%) was described in men. In 13 of 18 cases the disease was diagnosed at the stage of loco-regional advanced disease. All described patients underwent surgery and most of them survived more than 12 months.

In the presented case, gastric cancer with OGC was poorly differentiated. It was characterized by rapid growth, early metastasis and poor prognosis. The absence of EBV infection and lack of metaplastic bone formation units, negative staining for synaptophysin and infiltration by lymphocytic cells may suggest a non-LELC subtype. The rarity of this type neoplasm in clinical practice as well as very limited relevant literature data make it extremely difficult to arrive at universal conclusions about the prognosis in OGC gastric adenocarcinomas in comparison to other types of gastric carcinomas. Moreover, the function of OGC in tumor biology also remains unclear. This problem definitely needs further assessment on larger groups of patients.

**Conflict of interest:** none declared

**Kamil Wdowiak, MD**

*Silesian Medical University*

*Department of Internal Medicine and Oncology*

*ul. Reymonta 8, 40-027 Katowice, Poland*

*e-mail: wdowiak.kamil@op.pl*

*Received: 12 Mar 2018*

*Accepted: 8 Jun 2018*

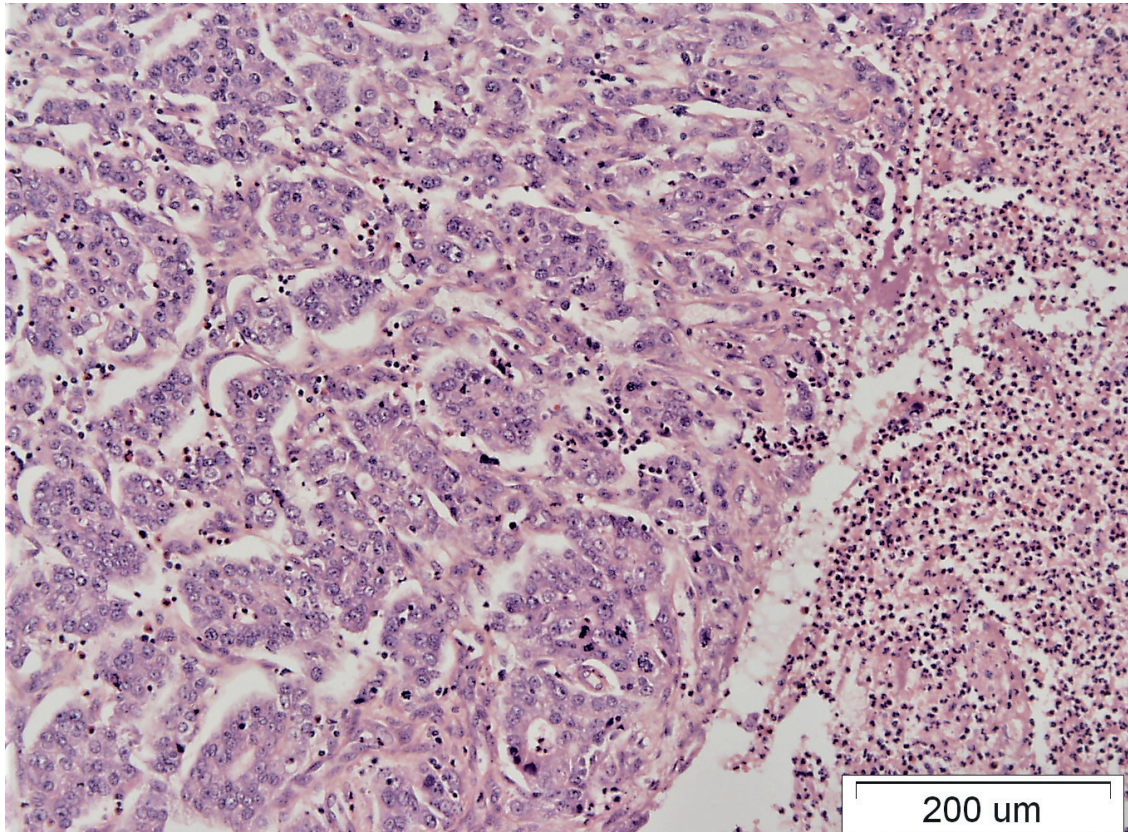
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## Appendix



**Figure 2.** Poorly differentiated adenocarcinoma of the stomach (H&E 200 um)